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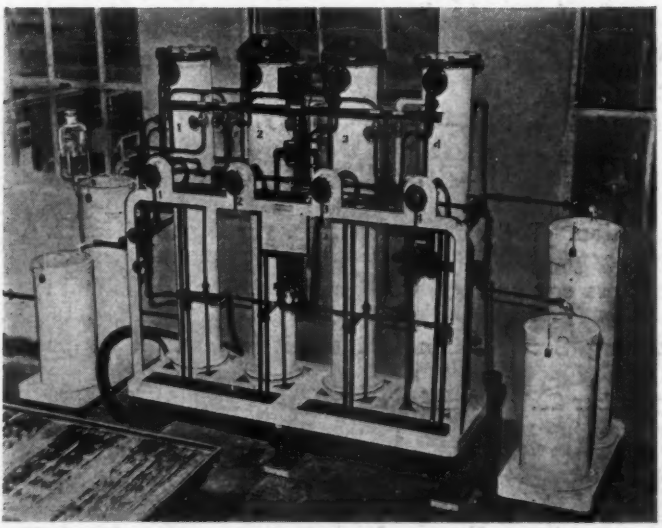

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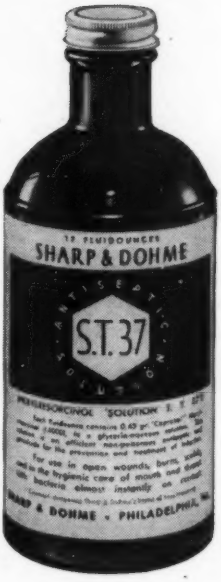

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CHRISTMAS, 1944

GREEN stands the tree in the frozen earth,
And green rots the flesh
In the hospital ward.

Red hangs the holly by the prickly leaves,
And red drops the blood
On the battlefield.

White shines the mistletoe, waxy white,
And white gleams the face
In the blasted home.

Shut not your eyes, but see to the bitter end:
For the blazing fire you casually tend,
See ashes that are blackened, and crumbling stone;
For the dinner you eat, too lazy to share,
See children hungry, afraid, and alone;
For the gifts you buy with thoughtful care,
See the corpses that lie, neglected bone.
For all the joys of love,
Of peace, security,
Of happy innocence,
And childlike faith,
See, too, the spawn of hate,
The monstrous brood that swarms
Over the shrinking earth:
Disease and filth and crime,
And every vile and revolting deed
That springs from the snake-tongued seed
Of beasts endowed with savage mind;
Take the toll of torture,
Of pain, fear, suffering,
Of immeasurable, bottomless, boundless woe,
Of broken bodies, homes, nations;

In the jungle scramble for land and trade,
See where the arts low trampled lie;—
Measure this horror round about,
Know its height and breadth and depth,
Look and look until surfeit
Brings its final, sickening close.

Christmas is an idle word,
A mockery of recurring time,
The jest of a forgotten legend,
The butt of a bookkeeper's ledger,
If, after two thousand years
The spirit of the Christ-child
Finds not its Bethlehem home.

This must be the story retold
(Or there will be no telling),
That there are true shepherds
Patiently guarding their flocks by night,
That angels can sing, a vision of light,
That wise men come travelling afar,
Who worship not at the shrine of war,
That the child lies in the manger, sleeping,
Sleeping, while the world waits, weeping,
Longing for the rebirth of love,
For the incarnation of hope.

When the child wakes on Christmas morning,
Then will come an end to mourning,
Then will leap men's hearts again,
Released from their burden of fear and pain.

Then green will grow the tree of faith,
And red will bloom the rose of love,
And white will shine a newer world.

MILDRED A. PURNELL.

E D I T O R I A L

VITAMINS—WORTHLESS OR VALUABLE?

IN a recent issue of the *Journal of the American Medical Association* a paper is presented which purports to show that the administration of vitamin supplements to apparently normal persons has no demonstrable beneficial effect. Considerable weight has been attached to this paper by the medical press as an argument that the use of vitamin products is totally unnecessary by the general public.

A perusal of this paper cannot but lead a critical analyst to the conclusion that the authors' conclusions have insufficient evidence to back them up. We do not argue that there is not a widespread abuse of vitamin data by unscrupulous advertisers, and it is a fact that many persons take vitamins who probably do not need them, but the experimental work in this paper is not fundamentally sound. In the first place, the test subjects selected were medical students and technicians. Persons in this category are invariably young, healthy individuals with a robust appetite, living under ideal environmental conditions, probably on the university campus. This is surely not a representative group of our total population. Secondly, the individuals from whom purely subjective symptoms were to be obtained knew the nature of the experiment although each did not know whether he was taking a vitamin product or a placebo. Now it is a well-established fact that all students are inclined toward cynicism, as any educator knows, and medical students in particular. The results could have been predicted in advance by any student of human psychology. Of course they did not feel better! Even if these students tried to be honest, the circumstances were such that they were predestined to report negative results. The situation was such that the subject not knowing whether he was receiving vitamins or placebo would as a matter of self-protection report no change since it was the only safe answer that was fully acceptable in any case.

The medical profession knows full well that the public can be treated for many "disorders" by simply giving capsules of milk sugar with miraculous results. Here the conditions are reversed. The

patient, having implicit confidence in the physician and no organic disease, is convinced that the medication will be effective and it is. The popularity of cold vaccines is probably due to the favorable psychologic effect they have on patients since controlled studies cast serious doubt on their value in reducing the incidence of colds.

There is ample evidence that vitamin supplements if properly constituted and administered are highly desirable. If they are not then the present program for enriched flour, originated by the National Research Council, was unscientific in its conception; this seems highly unlikely. One fact seems to be overlooked by those who so loudly condemn vitamin supplements. It is a well-established fact that mild vitamin deficiency is usually unrecognized even by the physician. Since the administration of a hexavitamin tablet or capsule a day can do no harm its widespread adoption is certain to include many individuals who otherwise might be suffering with a mild hypovitaminosis. Older adults with their fixed dietary habits and low calorie requirements are quite likely to need some auxiliary supplement of the vitamins as are many persons of sedentary habits. To embrace this group it is well worth the economic waste of widespread use of vitamin supplements since it is the only way of reaching those who need it. It is comparable to mass vaccination where many already immune are treated nevertheless. In our opinion the benefits derived far outweigh the argument that many or even a majority do not need it.

The current excesses in the advertising of vitamins should be controlled and they should be represented in their true light as simply prophylactics and not cure-alls. The paper referred to in this article neither refutes this concept of their usefulness nor should it discourage their use.

L. F. Tice.

FALSE RESIDUAL CHLORINE VALUES PRODUCED BY INSOLUBLE MANGANESE AND THE EFFECT OF ACTINASTRUM IN A WATER SUPPLY*

By George G. Schaut **

DURING the summer of 1936 the chlorinated water applied to the rapid sand filters showed O. Tolidine readings that were not in keeping with the quantity of chlorine added to the water. In general, the warm water of the summer season does not retain its residual as in the colder months. During this summer, instead of the chlorine values dropping off, the values were higher than expected. Suspicion was aroused, chlorine dosages and machine operation were checked to see if any defect existed at the point of application.

A sample of river water was then treated with O. Tolidine [1] and at the end of the five-minute period a color was present which could readily be matched by the chlorine standards. It thus became evident that a real interference, with the proper application of chlorine, was present in the raw water. When the raw water was filtered through a No. 42 Whatman filter paper and the filtrate tested with O. T., the color produced in the filtrate was almost *nil*, then upon moistening the residue on the filter paper with a few drops of O. T. a greenish yellow color immediately developed, thus indicating that the substance responsible for this reaction must be in suspension in the water. This is not unlike the phenomenon reported by Forsberg (1), who showed that manganese in surface waters gave a reaction with O. T. similar to chlorine and that unfiltered waters gave a positive reaction for chlorine, while those filtered through filter paper to remove the manganese produced no color when O. T. was added to the filtrate.

Besides manganese, iron and nitrites were recalled to the writer's mind as being possible interferences and these should be first ruled out, as both are present in our water supply. From a previous study of nitrite-O. T. reactions in various waters, the color production by

* Released for publication through the courtesy of Martin J. McLaughlin, Chief, Bureau of Water, City of Philadelphia, Pennsylvania.

** Chief Chemist, Philadelphia Water Bureau.

[1] Due to frequency of use in this paper of the reagent O. Tolidine, the author takes the liberty of substituting for it, as the occasion arises, the symbols O. T.

nitrites varies over a wide range. In some waters nitrites do not give a color with O. T., whereas in others the color production by nitrites when O. T. is added is just a little below the equivalent of the chlorine value, and can fall to one-half or even one-quarter the equivalent chlorine value. Since the nitrites are soluble in water, and iron up to 1 p. p. m. is of little significance, then manganese had to receive further study. Manganous sulfate solutions do not give a color reaction with O. Tolidine. The hydroxide was prepared using caustic soda and it was observed that unless kept from contact with air the flesh colored (pink) hydrate turned brown due to oxidation, thus forming manganic hydroxide, especially on a filter paper where the solid is spread out in a thin layer and comes in direct contact with the air. The manganous hydroxide did not give a color when moistened with O. T. reagent whereas the manganic gave the characteristic chlorine color. Since O. T. is ordinarily dissolved in water containing hydrochloric acid, one might be inclined to think that O. T. is actually reacting with chlorine liberated by the manganese acting upon the HCl; for the old well known process for making chlorine was to allow pyrolucite (MnO_2) to react with hydrochloric acid as shown by the following reaction.

$$MnO_2 + 4HCl \overset{\Delta}{=} MnCl_2 + 2H_2O + Cl_2$$

Here is observed manganese in the higher state of oxidation, liberating chlorine from hydrochloric acid.

In order to observe any effect that hydrochloric acid might have, it was decided to substitute for the hydrochloric acid in the O. T. reagent, acetic acid in the same concentration, i. e., 10 per cent acetic acid. This reagent, ½ cc. per 50 cc. of sample, reacted with both chlorine and manganese (*ic*) giving identical colors (blue-green). The shade is much more vivid than that from O. T. in hydrochloric acid. If one wishes to make up a set of standards for this color, the same chemicals may be used as when making standards for O. T. in HCl, only the quantities are quite different and the copper sulfate reagent must be 5 times the strength of that in "Standard Methods". The use of O. T. in acetic acid together with the corresponding standards was developed by the late Dr. George E. Thomas, then Director of our Laboratories, in order to overcome the interference due to nitrites. For a number of years chlorine determinations were made in parallel, using O. T. in HCl and also acetic acid, with

the result that the values were invariably within a couple hundredths of a part per million. So, for those caring to use O. T. in acetic acid the quantities of each reagent to prepare the standards are indicated in Table 1.

TABLE 1

Preparation of Permanent Standards for the Determination of Chlorine (c. c. of each reagent to be mixed and diluted to 50 c.c.)

Chlorine (p. p. m.)	Solution of copper sulfate *	Solution of potassium dichromate **
0.03	0.3	1.2
0.05	0.5	1.5
0.10	1.4	3.0
0.15	4.2	5.5
0.20	7.0	8.0
0.25	10.2	11.0

* Strength of reagent is 5 times that indicated in Standard Methods.
** Same strength as Standard Methods.

Hence, by the use of O. T. in acetic acid, hydrochloric acid as a possible source of chlorine was ruled out, for the insoluble manganese in water reacts with this reagent just as when HCl is used to prepare the O. T. reagent. Therefore, it is safe to proceed with the assurance that O. T. is a measure of the insoluble or *ic* manganese. Forsberg (1) entertained the same thought as to the effect of the solvents for O. T.; he showed that the common solvents, e. g., water, alcohol, sulfuric acid and hydrochloric acid, all gave the same reaction toward manganese. With all these facts in mind the investigation centered around the idea of *ic* manganese in suspension, but soluble manganese determinations would be easier to make and this value deducted from the total would give the insoluble manganese. For the purpose of filtering the samples, all were passed through No. 42 Whatman paper. The persulfate method was used for all manganese determinations. O. T. added to the filtrate usually showed *nil;* where a slight color did develop, it rarely exceeded 0.02 p. p. m. as measured on the chlorine standards.

Samples of water from various points along the Schuylkill River were obtained from time to time and the determinations are shown in Table 2. The *total* manganese shows no definite relation to the color recorded in terms of residual chlorine by O. T. If, however, insoluble

TABLE 2

Analytical Data on Schuylkill River Water at Belmont Intake

Date	8-11-36 [1]	8-11-36	8-12-36	8-28-36 [2]	9-14-36	9-21-36	9-24-36	10-5-36 [1]	10-19-36	11-17-36	9-14-36 [3]	7-19-39	7-21-39	7-24-39	6-26-39 [3]
Turbidity	17	13	9	16	17	14	12	12	12	12	17	40	34	40	17
Temp. C.	25	26	27	25	24	22	24	18	17	9	23	24	25	26	24
O. Tolidine reading [4]	0.28	0.12	0.12	0.01	0.20	0.08	0.20	0.05	0.02	0.02	0.05	0.18	0.15	0.10	0.06
Total Manganese	0.60	0.30	0.30	0.30	0.30	0.28	0.28	0.07	0.26	0.19	0.07	0.20	0.18	0.33	0.06
Soluble Manganese	0.30	0.20	0.20	0.30	0.10	0.18	0.15 [5]	trace	0.23	0.18	0.00	0.02	0.05	0.22	0.00
Total Iron	0.44	0.60	0.60	0.64	0.80	0.64	0.34	0.44	0.76	1.12	1.04	0.90	1.20	1.40	0.66
Nitrite—Nitrogen	0.016	0.032	0.036	0.040	0.028	0.032	0.064	0.014	0.035	0.030	0.032	0.032	0.028	0.048	0.004
Dissolved Oxygen (D. O.)	10.9	4.4	5.2	3.5	4.5	4.4	3.9	10.3	5.2	7.0	3.0	8.5	4.7	7.2	8.6
D. O.% saturation	130	54	64	42	53	50	46	108	54	60	34	100	56	88	101
Hydrogen Ion pH	P	7.7	7.5	7.2	7.5	7.4	7.4	P	7.2	7.1	7.0	P	P	P	P
Actinastrum St. Units	9700	5600	6800	0	180	27	10	20	0	0	16	26000	13000	26000	17000

The unit of measurement for turbidity, manganese, iron, nitrite and dissolved oxygen is the p. p. m.

[1] River at Norristown Dam.

[2] Sample collected after heavy rain flushed out the river.

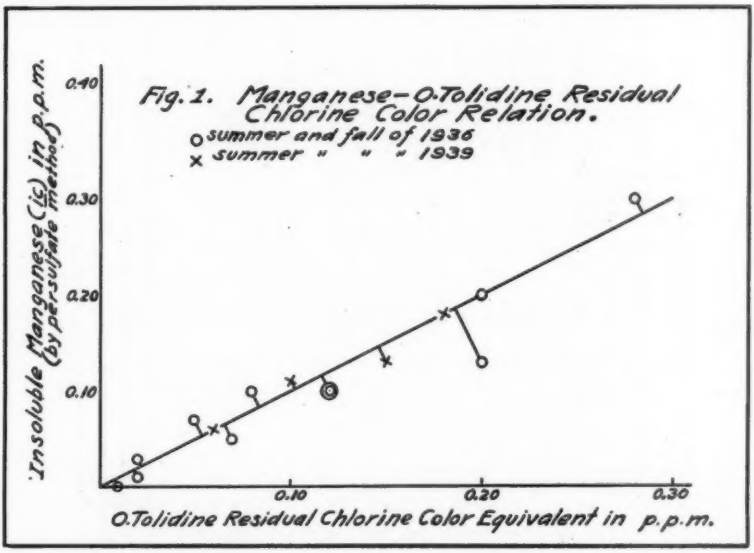
[3] Delaware River at Torresdale Intake.

[4] The O. Tolidine reading, is the color produced by this reagent and measured by a set of free chlorine standards reading in p. p. m.—hereafter stated as "equivalent chlorine", and it is not intended that the expression be considered in the bactericidal sense.

[5] Subsequent work on this filtrate showed it to contain an O. Tolidine value of 0.04 p. p. m. as "equivalent chlorine", so if 0.04 is deducted from 0.15 then the 0.11 represents the managn*ous* or soluble manganese. It appeared as if the 0.04 manganese was (*ic*) manganese in too fine a state to be retained by this particular piece of filter paper.

P Slight phenolphthalein alkalinity (no free CO_2).

values are plotted against the O. T. readings obtained just as the water is collected (no filtration nor sedimentation), then a very definite relation exists and is shown in Fig. 1. The points producing



this line fall close enough to it to show that O. T. is a direct measure of the insoluble manganese (*ic*) present. As any interference to the chlorine determination, when chlorination is practiced, becomes a serious operating condition, and could easily become a menace to public health, it soon behooves one to find a way of overcoming such interference. Enslow (2) suggested boiling as a means of removing the chlorine, whereas the manganese still remains to react with O. T. and for all practical purposes the O. T. residual chlorine color equivalent reading for manganese could be subtracted from the total O. T. reading (before boiling) and the difference was a measure of the free chlorine.

The present writer found this method to be quite suitable where most of the manganese is present in the insoluble manganic state. If, however, a considerable portion is present in the manganous state, then boiling, especially if the water is an alkaline water, oxidizes some of the manganous manganese to *ic* and O. T. reading then is higher

than before boiling. A phenomenon of this kind could be quite misleading in the case of a recently filtered chlorinated water, where all the manganese has not yet been oxidized to the *ic* state. If all the manganese is in the insoluble (*ic*) state, then one might assume that the boiling could cause no further change as far as manganese is concerned. This is not always the case, for in Enslow's article is mentioned the findings of Griffith at the laboratories of the North Jersey Water Commission located at Wanaque, i. e., boiling sometimes made a sample give a lower color reading with O. T. than the unboiled, when, of course, no chlorine was applied. To the present writer this is not surprising, for any change in the state (chemical and/or physical, i. e., colloidal) of manganese will undoubtedly vary the color intensity to be observed when O. T. is added.

The oxidation of small quantities of manganese by post-chlorination (0.10 to 0.20 p. p. m.) and aeration is not an immediate reaction. Filtered, chlorinated water containing manganese (*ous*), upon long standing, will then give a color when O. T. is added, due to slow oxidation of the manganese that was not removed by filtration. In Table 3 are values obtained after the filtered, chlorinated water, from

TABLE 3

Final Effluent of Filter Plants after the Chlorine Disappeared

	Equivalent Chlorine in p. p. m. obtained by O. Tolidine		Manganese (p. p. m.)	
	U. F.	F.	U. F.	F.
Torresdale	trace	0.00	0.00	0.00
Upper Roxborough	0.01	0.00	trace	0.00
Queen Lane Slow Sand	0.01	0.00	0.00	0.00
Queen Lane Rapid Sand	0.12	0.00	0.10	0.00
Belmont Slow Sand	0.01	0.00	0.07	0.06
Belmont Rapid Sand	0.05	0.00	0.13	0.08

U. F. represents water before being filtered in laboratory.

F. is water after filtering through No. 42 Whatman paper and any manganese present is in the soluble form, i. e., *ous*.

the various plants, has stood in the laboratory for about a month and bottles shaken from time to time to effect aeration, as well as, remove the free chlorine. Incidentally, this table shows the ability of the respective filtration processes to remove manganese from the water.

Other lines of approach, as to overcoming the manganese interference, presented themselves, e. g., (1) centrifuging and (2) filtration. To be of use both of these must remove the suspended manganese and at the same time not cause any chemical change of the manganese and, all important, allow the chlorine to remain in the water undiminished.

For centrifuging, 100 cc. samples were whizzed at 2000 R. P. M. for ten minutes and the upper 50 cc. removed into 50 cc. Nessler tubes and ½ cc. of O. T. added, then reading the color at the end of five minutes. Another portion similarly treated had the manganese determined in the uppermost liquid. In conjunction with this work, O. T. and manganese determinations were run on unfiltered and filtered portions using No. 42 Whatman paper. Comparative values are shown in Table 4. In this table it is to be observed that filtering

TABLE 4

Filtering, Centrifuging—Their Effect upon the Suspended Manganese as Measured by O. Tolidine

	Equivalent Chlorine in p. p. m. obtained by O. Tolidine		Manganese (p. p. m.)		
	U. F.	F.	U. F.	F.	C.
Water (a)	0.12	0.00	0.10	0.00	0.00
Water (b)	0.02	0.00	*0.07	0.05	0.07
Water (c)	0.15	0.00	0.14	0.00	0.00

C. column shows values for water after centrifuging and when a 50 c. c. portion of these centrifuged samples was treated with O. Tolidine no color developed.

and centrifuging are in close agreement. What happens to the chlorine by whizzing was next observed by taking a natural filtered water containing no manganese and no chlorine, adding chlorine water to it so as to produce a residual of 0.11 p. p. m.; then, after centrifuging, the chlorine was found to be 0.09 p. p. m. This was again repeated, making the initial chlorine concentration much higher, i. e., 0.45 p. p. m. and then after centrifuging, the value was observed to be 0.42 p. p. m. As a further attempt to evaluate this method, a portion of the same waters as used to produce data in Table 4 had chlorine added to them so as to establish a residual of 0.23 p. p. m. and then centrifuged. The O. T. and manganese determinations upon the uppermost liquid are shown in Table 5. Water (a) shows 100 per cent

TABLE 5

The Effect of Centrifuging upon Free Chlorine in Water with and without Manganese

	Chlorine* (p. p. m.)	Manganese (p. p. m.)
Water (a)	0.23	0.00
Water (b)	0.28	0.07
Water (c)	0.28	0.00

* As measured by ortho-Tolidine.

retention. Unfortunately, water (b) contained manganese in forms that might account for some of this discrepancy. Water (c) having no soluble manganese is as yet unexplainable, unless one analyzes the method and figures, e. g., the usual range of chlorine standards, especially in the high values, does not permit direct readings to the hundredth part. It is customary to estimate between standards so that it is possible to have an error in reading of $\pm$ 0.02 p. p. m. for a single reading. In making observations before and after a certain operation, it is not impossible to have the errors of such an order that they produce figures at relatively wide divergence. By the same token, the reverse of this is also possible, then $0.28 - 0.04 = 0.24$ and 0.23 was actually added. These values, although not exactly equal before and after centrifuging, are certainly in close agreement from a practical standpoint. It appears that centrifuging does not throw out the chlorine and will throw out the insoluble manganese.

The filtration idea using filter paper was not given study in the laboratory, for it was realized that paper has a "chlorine demand." Some filter medium must be used that either has no demand or such as can easily have its demand satisfied. To accomplish this requires a minimum of material used as the filter medium. The Sedgwick-Rafter plankton filter set-up was adopted using a ½ inch depth of washed sea sand supported by a small piece of bolting cloth contained in a glass funnel of 250 cc. capacity with graduations every 50 cc. With this apparatus it was easy to satisfy any "chlorine demand" of an inherent nature.

Method used. Poured 250 cc. water into filter funnel and allowed 100 cc. of filtrate to go to waste, then added 100 cc. more of sample and then collected next 100 cc. of filtrate and set aside for a manganese determination. The following 50 cc. were collected in a Nessler tube and one-half cc. of ortho-tolidine added. The samples tested were of varied character as may be seen from the following description and are listed by numbers in Table 6; (1) raw river water

TABLE 6

The Equivalent and Actual Chlorine Relation to the Manganese in Various Waters

	Equivalent and free Chlorine in p. p. m. by O. Tolidine		Manganese (p. p. m.)	
	U. F.	F.	U. F.	F.
Sample No. 1	0.02	0.04	0.60	0.60
Sample No. 2	0.15	0.12	0.60	0.56
Sample No. 3	0.04	0.04	0.60	0.60
Sample No. 4*	0.01	0.01	trace	trace
Sample No. 5	0.01	0.02	0.60	0.60
Sample No. 6	0.13	0.11	0.46	0.44
Sample No. 7	0.13	0.13	0.60	0.60

* As no chlorine is used in water before slow sand filtration and none added immediately after, the values obtained by O. Tolidine really measure the small amount of manganese (*ic*) as reported by a trace. A trace in this work refers to less than 0.01 p. p. m.

with a turbidtiy of 20 p. p. m., (2) applied water to rapid sand filters with a turbidity of 12 p. p. m. (3) effluent of rapid sand filters with a turbidity of zero, (4) effluent of slow sand filters with a turbidity of zero, (5) applied water to slow sand filters with a turbidity of 18 p. p. m., (6) applied water to rapid sand filters (at a different plant than No. 2) with a turbidity of 4 p. p. m., (7) a water from a rapid sand plant just as the water goes to distribution. In samples 2, 3, 6 and 7 the values obtained by O. T. and shown in column (F.) represent the true chlorine (free) content of the water. From this table it appears as if O. T. is again a measure of the insoluble manganese (*ic*) and when insoluble manganese and chlorine are present together, then filtration through the Sedgwick-Rafter apparatus removes the insoluble manganese (*ic*) and not the chlorine (after the chlorine demand of the apparatus has been satisfied).

If this method is applied to waters having a *low* temperature and high dissolved oxygen content, then in a warm laboratory, air bubbles collect on the sand grains as the water is being filtered. This is due to the rise in temperature of the water, thus creating a supersaturated condition. Water containing chlorine while passing through this medium of sand and air has its chlorine content somewhat diminished. This does not occur if the water temperature and D. O. content are such that supersaturation of the water is not produced by the warm laboratory. Maintaining the entire apparatus at a temperature

approximating that of the water does not permit this supersaturated condition to form and the chlorine values before and after filtering are practically the same. This precaution is probably of little significance, for most of the manganese interference occurs in the warm months.

In a very illuminating study Chamberlin and Glass (3) have recorded their findings as to the O. T.-chlorine colors. Suggested procedure is of a more scientific nature and gives less interference due to iron and nitrites. Hallinan (4) of rather recent date records maximum values for interfering substances giving a color with O. T. By a selective procedure with O. T. and arsenite, he overcomes what has been a perplexing problem and obtains values for active residual chlorine and chloramine.

Microörganism—Oxygen Saturation Relation

As it is customary to test all waters coming into the laboratory for pH it was soon discovered from the very first sample (see Table 2) that the water had a phenolphthalein alkalinity of several p. p. m., i. e., no free carbon dioxide. As a rule the river in the summer does not show this condition. Dissolved oxygen determinations were also done, with the result that oxygen saturation values above 100 per cent were found. Surely, this is not to be expected in this river during the summer, for ordinarily if the river has 40-50 per cent saturation it is considered in good condition. With phenolphthalein alkalinity and high oxygen present, one immediately suspects algæ and hence microscopic examinations also were included. Strange as it may seem, one organism of the Chlorophyceæ group was always present in excessive numbers when the oxygen saturation value hovered around 100 per cent. This condition as to high oxygen values did not persist long, but it gave us a start to know what to look for in the future. The organism is not a single plane body. Its structural form somewhat resembles the metal jack stone used by children for playing the game bearing this name. The organism is named *Actinastrum* and Smith (5) gives a brief account of it. Three varieties are shown in Smith's Treatise.

The organism as observed by the present author is not identical to any of these forms but more closely resembles that of Lagerheim. Characteristics observed by the present investigator using low power magnification are recorded as follows. Coenobes composed of 4, 6 and

8 elongated cells that radiate in all directions from common hub. The individual cells have a diameter of about 5μ and a length about 5 times the diameter. Under higher magnification ($\times$ 1700) the elongate cells were blunt and cytioderm was colorless and smooth encasing light green chloroplast. No pyrenoid bodies were seen but the chloroplast was noted to be interrupted all the way across its greatest transverse section, thus making two perfect halves of chloroplast in each elongate cell. This organism might be called *Actinastrum schuylkillensis-delawareensis,* or for short, dubbed *Actinastrum philadelphica.*[2]

Although manganese interference appears every year during the summer, its severity is governed by the flow (volume) of the river, as dilution is an important factor. It probably has been in the Schuylkill River for a very long time, but only became a factor when prechlorination was practiced, and the chlorine residual had to be determined. The high oxygen content of the river in summer does not appear every year and for the first time (summer of 1936), during the author's experience of eighteen years, its appearance was detected and also the presence of *Actinastrum* in excessive numbers. Its recurrence was not again detected until the summer of 1939. No doubt this excessive oxygen content is a factor in rendering the soluble manganese insoluble. Very early in the summer of 1939 a sample of water taken from the Delaware River at the intake of our Torresdale Filtration Plant showed phenolphthalein alkalinity and immediately a microscopic examination and dissolved oxygen determination were made. Results as noted in Table 2 were obtained. A sample taken the very next day from the same point failed to reveal this condition. This is not unusual, as the Delaware River at Philadelphia is a tide-water stream. Noting this condition in the Delaware is like snapping some eclipse that occurs infrequently, i. e., sometimes you get it and sometimes not, and a few hours make a big difference. This condition in the Delaware River, to the best of my knowledge, has never been detected before and did not occur again during the summer and fall of 1939. During the summers of 1943 and 1944 a small number (not sufficient to materially raise the oxygen content) was found in the Delaware River. They have not appeared in the Schuylkill River since the summer of 1939.

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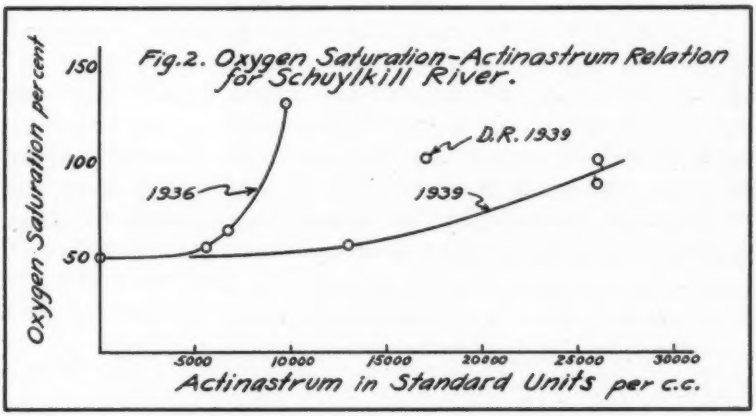
[2] These three Latin subfixes are not original with the writer, having been coined by the writer's kind and helpful friend Dr. Ivor Griffith, President of the Philadelphia College of Pharmacy and Science, and used with his permission.

The relation between oxygen saturation and the organism is best illustrated by the curves in Fig. 2. It is quite apparent that it took



almost three times the number of organisms during the recent occurrence to produce the same oxygen saturation as three years ago. Both summers were mild drought periods, whereas, during the intervening years the river had a flow above normal for the summer period. The difference in these two curves should represent the ability of the body of water to utilize oxygen and could easily be a rough measure of the stream's B. O. D. However, since these conditions do not exist nor spread out over a wider period of time and do not recur each year, it would be desirable to not place too much emphasis upon these curves until subsequent observations place more points on them. The single observation for the Delaware River is shown in this figure and surely indicates that there must be a difference between waters.

Microörganism—Fish Relation

During the time this organism was in the river, natives along the stream said that fishing was poor—"they just wouldn't bite". Without knowing what was present in the water, these "followers of Izaak Walton" believed the fish wouldn't bite because something in the water made their mouths sore. No dead fish were seen along the stream, but something in the way of laboratory data was obtained in

that four test minnows were placed in an (40 liter) aquarium having water flowing through it at the rate of 2 liters per minute. The water was taken directly from the river and its analysis is shown in Table 2 under date of 7-19-39. The total alkalinity of the water was 75 p. p. m. with a phenolphthalein alkalinity of 6 p. p. m. The next day all fish were alive but they were rather reluctant about eating. The fish were left in the water another day, making a total of forty-eight hours and then removed to stabilized tap-water, at which time they appeared perfectly normal and then ate freely. Several days later these test minnows were still alive in the stabilized tap-water, so, if any injury is sustained by fish in water having such an unusual character it certainly is not permanent.

Summary

The reaction between O. T. and insoluble manganese (*ic*) is not due to the hydrochloric acid used in preparing the reagent.

A set of standards is described for the determination of free chlorine when using O. T. in acetic acid.

A definite relation exists between insoluble managanese (*ic*) and the color it produces with O. T. when this color is measured by the usual range of chlorine standards and expressed as free chlorine; in other words, it seems as if this form of manganese has the same oxidation potential as free chlorine in water, when measured by O. T.

Two methods are given for the quantitative estimation of insoluble manganese (*ic*) in water, in the presence of free chlorine, by using O. T.

A microorganism of the Chlorophyceæ Group was found that was the cause of high oxygen values in a stream, even to supersaturation, and at the same time leaving no free carbon dioxide present.

Conclusion

Manganese in streams, if the natural conditions are favorable, may present a serious interference to the proper operation of a filter plant where chlorine is used (pre or post) by giving a false residual when O. T. is used—this in turn giving one a false sense of security. Numerous investigators have reported on the interference of manganese and many attempts have been made to evaluate it in terms of chlorine and the first part of this paper is only another attempt to

do just that. Relatively large quantities of manganese do not appear to be necessary for the existence of *Actinastrum* as evidenced by the Delaware River sample.

Actinastrum in excessive numbers produce high oxygen saturation values in a water that ordinarily would not be high. It appears as if a rather definite relation exists between the organisms and the oxygen saturation. The experimental work does not definitely prove that these organisms are harmful to fish but some disturbing influence is present at the time these organisms are present. This may not be due directly to the organisms but their metabolism. By taking in CO_2 and liberating oxygen, perhaps the oxygen or some part of it, is at first liberated as nascent oxygen. Hubbs (6) has shown that only a very small quantity of nascent oxygen need be present to affect fish. Surely, it is not due to lack of CO_2, for the present writer has kept minnows in water containing several parts per million of phenolphthalein alkalinity (carbonate) for 48 hours without being able to detect any visible effect upon them.

Acknowledgment

The author wishes to express his sincere appreciation to the members of the Laboratory Staff and River Patrol for their many helpful suggestions, also their contribution of time and effort by relieving the writer of some of the detail work during this investigation.

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TRENDS IN DRUG THERAPY WITH A NOTE ON PHYTOLACCA

By Samuel W. Goldstein *

MAN'S early writings contain many references to the uses of various agents for altering undesirable conditions of the human body. Existing primitive peoples have their crude forms of medical practice and practitioners. The treatments instituted by the early medicine men no doubt were in many cases responsible for the deaths of patients suffering from minor but painful ailments, such as indigestion after too much raw tiger meat. Also during the past several centuries the more civilized and learned physicians' practice of bloodletting no doubt hastened many an introduction to St. Peter for individuals who really required more blood. Of course many of the early drugs, among which were excreta, cobwebs, molds, and any vile-smelling substance at hand, had beneficial action in some cases. In fact, we are still using some of the substances, and constituents of others, that were used centuries ago.

Although medicinals and medicinal preparations such as ointments are found in Egyptian writings from 2,000-3,000 B. C., Galen, who lived in the second century A. D., is given credit for devising and making popular the liquid preparations of vegetable drugs known today as galenicals. Paracelsus (1493-1541), a Swiss physician and alchemist, introduced iatrochemistry, which advocated the use of chemical in place of vegetable remedies. He had plenty of opposition in those days, but he was successful in pointing the way to the use of pure substances in therapy, and is credited with being the father of pharmaceutical chemistry.

The beginning of the nineteenth century saw a growing interest in the constitution as well as the therapeutic classification of plants. Courtois, a French chemist, in 1811 discovered iodine in the ashes of seaweed. Derosne in 1803 isolated a crystalline material from opium, the basic nature of which was recognized by Sertürner in 1806 who named it morphine after Morpheus the god of sleep. Sertürner's work was almost unnoticed until he published a second paper in 1817. Between 1817 and 1835 twenty-six different alkaloids were

* Pharmaceutical Chemist, Maryland State Department of Health.

isolated, including the widely used strychnine and quinine by Pelletier and Caventou (1818 and 1820), caffeine by Runge (1820), atropine by Geiger and Hesse (1831), and codeine by Robiquet (1832). (1) The number of alkaloids isolated from plants or synthesized is now in the hundreds, and many of them have eliminated the use of the crude drugs and their galenical preparations.

The use of therapeutically active synthetic organic chemicals was greatly stimulated by the discovery by Cohn and Hepp (1886) that aniline has powerful antipyretic and antineuralgic action, and that acylation to form acetanilid renders the compound much less toxic. (2) Acetanilid was included in the 1890 edition of the U. S. Pharmacopœia. Ehrlich (1854-1915), a German biochemist, and his coworkers synthesized arsphenamine (606) in 1909 and reported on its specificity in the treatment of syphilis in 1910. (3) He is considered to be the founder of modern chemotherapy, which is the study of the changes in biological activity of compounds caused by altering the positions of groups in the molecule and by changing the groups present, especially in side chains. This scheme was used in developing the homologues of barbituric acid and adrenaline and ephedrine. Many medicinal compounds continued to be synthesized, but not much was heard of the term chemotherapy until its violent resurgence with the introduction of the sulfonamides, when hundreds of molecular variations of the original sulfanilamide were prepared and tested.

A milestone in the battle of man against disease was the evolvement of the bacterial concept by Pasteur (1822-1892), and the introduction of vaccination by Jenner (1749-1823) and vaccines and antitoxins by Pasteur. These were great advances in the field of preventive medicine, a field that still needs cultivation in this country in spite of the fact that we have one of the most advanced groups of medical men in the world.

Practically all our preventive medicine is carried on by public health agencies which try to protect individuals by mass vaccination and inoculation, by purification of water supplies, enforcement of the food and drug laws and industrial health regulations. The private physician, in his desire to treat the patient, still ignores the benefits that would accrue to both doctor and patient if a little consideration were given to emphasizing and employing preventive procedures.

The preventive values of vaccines and antitoxins were vividly demonstrated in World War I when the loss of men through disease

was less than the loss in actual combat; and together with the antimalarial drugs quinine and quinacrine or atebrine, the bacteriostatic and bactericidal agents such as the sulfonamides and penicillin (against gram positive organisms) and streptothricin (against gram negative organisms), the delousing agents like DDT (dichlorodiphenyl-trichloroethane), repellants and other agents, even more spectacular results are being recorded in the present conflict. Furthermore, the greatly increased use of blood plasma and blood as therapeutic agents has saved many lives.

The advance of drug therapy can be summed up in the statement that the trend has been towards pure compounds with a better understanding of the pharmacodynamic behavior of medicinal agents.

In spite of great strides in drug therapy and medical practice, the oldest form of treatment, that of self-medication, flourishes. A recent report on the work of the Council on Pharmacy and Chemistry of the American Medical Association (4) contained the following excerpt: "The proprietary medicine business is essentially a development of the last seventy years. Nostrums placed on the market in the seventies and patented German synthetics became enormous in number in the early part of this century. Profits were immense and enticing. While a few of the compounds were of distinct value, the vast majority were simple mixtures of well-known drugs put out under fanciful copyrighted names and for the most part fraudulent in one way or another; many were actually dangerous. Some were products from well-known drug houses; the majority were put out by men who knew nothing of drugs or their effects but who went into the business of manufacturing medicines as they would any other business. Few hired competent chemical or medical advice, and as a result no statement was too silly or claim too extravagant. Those with a critical eye should have seen through the flimsy material offered as 'evidence,' but by persistent and occasionally clever advertising many were duped into buying and using these mixtures. Truly in these earlier days medicine in some instances could have been defined by the disappointed patient and physician as 'the act or science of amusing a sick man with frivolous speculations about his disorders, and of tempering ingeniously until nature either kills or cures him.'" The kindest thing that can be said for amateur diagnosing and prescribing is that the proprietary medicine usually does not hurt the individual. The public is further protected by the

labeling requirements of the Federal and State Pure Food and Drug Laws if they wish to avail themselves of this protection. The bad feature of the practice of self-medication is that an individual may try remedies which do not help his condition while he becomes steadily worse before finally calling a physician.

Vitamins, those food essentials or therapeutic agents, depending upon the condition of the individual receiving them or whether you happen to be on the legislative committee of the grocers' or physicians' association, have received so much publicity that the vitamin-conscious public paid out $140,000,000 for them to the drug industry in 1943. Thirty-three per cent of that amount was paid to manufacturers who advertise directly to the public, the other 67 per cent going to the so-called ethical manufacturers who depend mainly on physicians prescribing their products. (5) This seems to be paradoxical, since the official publications of the medical profession denounce the widespread use of vitamins without medical supervision.

Recently the president of the American Medical Association decried the insufficient training given to students in the pharmacology courses of many medical schools. (6) He found that students frequently are not taught to choose a specific drug for a specific disease and symptom, and that not enough emphasis is given to training in prescription writing. In 1943 230,000,000 prescriptions were filled in spite of the shortage of civilian physicians and the claimed shortage of pharmacists. He stated that there should be no surprise at the ease with which many physicians can be persuaded (by detail men) that a different new product is best in the treatment of certain ailments, regardless of the many differences among the suffering individuals.

Many drugs are dispensed only upon presentation of a proper prescription, supposedly because the pharmacist is not capable of observing the necessary safeguards during the administration of these medicinals. In the case of sulfa drugs, when large doses are given, the concentration of the drug in the blood should be checked in addition to observing the general reactions of the patient. Many physicians prescribe these drugs and forget about the patient until the next visit unless unusual reactions are called to their attention. Certainly an important advance in drug therapy will be made when clinical laboratories are made readily available (and without charge) to all physicians. This will be especially important in the develop-

ment of the ideal role of the physician as the practitioner of preventive medicine rather than as a reliever of unpleasant symptoms after the individual has become ill.

The reason for including phytolacca in this discussion is that it may serve as an example of that group of substances which are given official recognition on the basis of their common usage at some period even though modern studies can show no definite value in their continued use.

Phytolacca or poke is a native American plant which was carried to Europe in the seventeenth century and was cultivated in France for its purplish red berries which were used to color Bordeaux wine. The plant was used by the American Indians, and the white foreigners used it for many years before it was introduced into professional practice. The early settlers used the mature plant as a poultice for inflammatory conditions of the cow's udder in the disease known as garget. The young shoots are similar to asparagus and are prepared for eating in the same manner. The mature plant was used domestically in the form of a tincture, and in 1820 was made an official drug in the United States Pharmacopœia, where the root was included in the Primary List and the berries were placed in the Secondary List. Both root and berries were official in the New York edition of the U. S. P. 1830, but were in the Secondary List of the 1830 Philadelphia edition of the U. S. P. They appeared in the Secondary Lists of the succeeding Pharmacopœias until 1880, when they were made wholly official and remained so until the revision of 1910 when they were deleted. Poke is a hardy plant and the root turned up as an official drug in the fourth edition of the National Formulary in 1916. The tentative plans for the eighth edition of the National Formulary call for the deletion of phytolacca along with about 190 other drugs or nearly one-third of the N. F. VII monographs. Apparently in this instance the trend in careless recognition of drugs is being violently reversed.

Now let us see what basis existed for the long period of recognition for this drug as a therapeutic agent. The use of the root in poultices was a logical development, for the root contains a large amount of gum and starch and when cooked forms a mush; furthermore, bread was too precious to be so used, and potatoes were unknown in North America at the time. Mitchell, who in 1850 wrote a medical treatise which was highly regarded for many years, treated

children's itch by placing the child in a bath of a strong decoction of the root and rubbing the skin for ten minutes. No doubt his treatment was beneficial for the decoction or boiling gave a sterile mixture containing enough saponin to produce a detergent action, and a hot salt solution to stimulate epidermal osmosis in addition to a local irritation and stimulation. The Italians used a strong decoction of the root for scrofula and syphilis, which undoubtedly aided in the spread of disease by people who thought they were cured or being cured. An eclectic resinoid is still used by some people in rheumatic and syphilitic conditions. Holmes (7) in 1920 wrote of the root that it is a useful remedy in the treatment of cancer and ulcers. The only definite claims made for the drug are such that one is led to believe that the main reason for recognizing phytolacca as an official drug was the pressure applied by manufacturers of nostrums, many of which contained the drug along with their other "shotgun" ingredients.

While any claim to therapeutic value for phytolacca is extremely doubtful, the toxic nature of the root is definitely established. Cressler (8) in 1875 reported poisoning accompanied by vomiting and purging in five persons while milling the drug. A 1937 publication (9) reports that two students engaged in milling some poke root subjected themselves, in spite of warning, to accidental inhalation of the drug dust. Both developed very severe respiratory irritation and gastro-enteritis, one individual requiring hospitalization. More than twenty-five occupants of the six floors of the same building (University of Maryland School of Pharmacy) developed similar symptoms of varying degrees of severity, a considerable number being forced to discontinue their regular activities for several days.

Although a number of reports on the presence of alkaloid in phytolacca were published, Burt E. Nelson (10) stated that the drug contains no alkaloid, and a later publication (9) stated that chemical and pharmacological tests indicated the absence of alkaloid, but the presence of substances (possibly plant proteins) which give amorphous precipitates with alkaloidal reagents was corroborated. The most toxic constituent of the plant is a resin-like substance, isolated from the root, which is fatal to cats when 32 mg. per Kg. is injected intraperitoneally. The substance has an ascending depressant action on the cerebro-spinal axis of cats, and more than one-half the toxic dose may be given with only slight action resulting.

This would not allow for safety even if the pharmacological effect were desirable.

Thus we see that a drug has been recognized in the official compendia for 125 years, enjoying legal status for almost forty years of that time though no scientific data warranted its retention.

Here and there we find the general trend from old to new reversed. The early Greeks and Romans thought highly of garlic and onions not only for the restoration of health but to maintain it. After a long period of neglect as medicines, Russian scientists are demonstrating the value of these vegetables. Cato in the second century B. C. recommended mashed cabbage as a treatment for healing bruises. Bacteriologists are now showing the germicidal properties of cabbage juice. Many people have claimed that their grandmothers (I haven't seen any claims for granddad) used bread mold on cuts and wounds long before Fleming noted its germicidal product, penicillin. But even in these instances we are not satisfied with the substance as used long ago but are ever striving to isolate, purify, synthesize and control.

In closing, a cautious yet hopeful tone may be added to what at present appears to be a very bright picture of therapeutic achievement. The main medical contributions of the ancient Arabian physicians were the therapeutic agents such as camphor, ergot, and senna, which they added to the materia medica; while that which the Arabs themselves regarded as their chief service, namely, the very careful determination of the drugs to be used for each disease and each "temperament" so that the physician after making the diagnosis could not go wrong in the treatment, is no longer valid. The Chinese have long used livers of fat fish in the treatment of tuberculosis conditions and were prescribing liver in large doses in the treatment of pernicious anemia before its recognition elsewhere. They used the drug ma huang (*Ephedra sinensis*) for centuries before ephedrine was isolated from it. But it may be that their greatest therapeutic contribution is the attention that the Chinese physician pays to the social and psychic factors entering into the causation of illness.

After Pasteur's work was fully recognized, many believed that all that remained was for the bacteriologists to find the organisms responsible for all diseases and prepare the corresponding vaccine or antitoxin to rid the world of disease. About 1920 the biologicals were the therapeutic agents that were to perform wonders; then along

came the sulfa drugs to overshadow the biologicals, and, more recently, a new drug which was then in the experimental stage. This new drug was not to be denied, and, after having its "arrival" delayed, penicillin now holds the spotlight along with streptothricin, tyrothricin and other new therapeutic agents.

We may hope that discoveries inconceivable to us at present may make what we think is a bright therapeutic era only the dark background upon which a truly brilliant picture is still to be achieved.

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PENICILLIN: THE INDICATIONS, CONTRA-INDICATIONS, MODE OF ADMINISTRATION AND DOSAGE*

PHYSICIANS who desire to employ sodium salt of penicillin, in the treatment of conditions hitherto not amenable to or resistant to therapy with sulfonamide drugs or other agents, should be guided by the following summary.

This report has been prepared by Dr. Chester S. Keefer, chairman of the Committee on Chemotherapy of the National Research Council and Consultant to the Office of Scientific Research and Development. It is based upon a study of over five thousand cases which have been reported to him, covering experience gained by clinical teams and physicians in a number of institutions. This large series of carefully controlled and reported cases has resulted in authoritative data upon which to base recommendations as to indications, contra-indications, mode of administration and dosage of penicillin.

In releasing penicillin for controlled use in the civilian practice of medicine, the War Production Board through the Civilian Penicillin Distribution Unit desires to make penicillin available to the greatest number of patients to whom its administration is justified without wasting material. Therefore it recommends Dr. Keefer's summary as a guide for treatment with penicillin in hospitals and institutions.

The text of the report prepared by Dr. Keefer, representing the recommendation of the Office of Scientific Research and Development and the National Research Council, follows:

"Based upon the experience gained in the past years with penicillin therapy, it has been found that penicillin is the best therapeutic agent available for the treatment of certain conditions, as follows:

"GROUP I INDICATIONS—

"1. All *staphylococcic infections* with and without bacteremia:
Acute and chronic osteomyelitis
Carbuncles—soft tissue abscesses
Meningitis
Cavernous or lateral sinus thrombosis

* From release of Civilian Penicillin Unit, War Production Board, 226 W. Jackson Boulevard, Chicago 6, Ill.

Pneumonia—empyema
Carbuncle of kidney
Wound infections—Burns
Endocarditis

"2. All cases of *clostridia infections:*
Gas gangrene
Malignant edema

"3. All *hemolytic streptococcic infections* with bacteremia and all serious local infections:
Cellulitis
Mastoiditis with intra-cranial complications, i. e., meningitis, sinus thrombosis, etc.
Pneumonia and empyema
Puerperal sepsis
Peritonitis
Endocarditis

"4. All *anærobic streptococcic infections:*
Puerperal sepsis
Localized infections elsewhere

"5. All *pneumococcic infections* of:
Meninges
Pleura
Endocardium
All cases of sulfonamide-resistant pneumococcic pneumonia

"6. All *gonococcic infections,* especially those complicated by
Arthritis
Ophthalmia
Endocarditis
Peritonitis
Epididymitis

"7. All cases of *Anthrax.*

"8. All cases of *chronic pulmonary suppuration* in which surgical treatment is contemplated.

"9. All *meningococcic infections* failing to respond to sulfonamides.

"10. All cases of *bacterial endocarditis* due to susceptible organisms.

"INDICATIONS IN GROUP II—

"Penicillin has also been found to be an effective agent in the following diseases but its position has not been definitely defined:

"1. Syphilis
2. Actinomycosis
3. Diphtheria, especially in horse serum sensitive patients

"CONDITIONS IN GROUP III OF QUESTIONABLE VALUE—

"Penicillin is of questionable value in mixed infections in which the predominating organism is of the gram negative flora, i. e.:

"1. Ruptured appendix with peritonitis
2. Liver abscesses
3. Urinary tract infections
4. It is also of questionable value in rat bite fever due to streptobacillus moniliformis

"GROUP IV CONDITIONS CONTRA-INDICATED—

"Penicillin is *contra-indicated* in the following cases because it is ineffective:

"1. *All gram negative bacillary infections:*
   Typhoid Para-typhoid
   Dysentery
   E. Coli
   H. Influenza
   B. Proteus
   B. Pyocyaneous
   Br. Melitensis (undulant fever)
   P. Tularense (tularemia)
   B. Friedlander
2. Tuberculosis
3. Toxoplasmosis
4. Histoplasmosis
5. Acute rheumatic fever
6. Lupus erythematosis diffuse
7. Infectious monunucleosis

8. Pemphigus
9. Hodgkin's disease
10. Acute and chronic leukemia
11. Ulcerative colitis
12. Coccidiomycosis
13. Malaria
14. Poliomyelitis
15. Blastomycosis
16. Non-specific iritis and uveitis
17. Moniliasis
18. Virus infections
19. Cancer

"TREATMENT OF INFECTIONS WITH PENICILLIN—

"The recommendations put forth in Dr. Keefer's report, based on the wide experience gained under varied conditions of use and purpose, follow:

"METHOD OF PREPARING PENICILLIN FOR TREATMENT—

"Penicillin is supplied in ampoules and vials of 100,000 units each. Inasmuch as penicillin is extremely soluble, it may be dissolved in small amounts of sterile, distilled, pyrogen-free water, or in sterile, normal saline solution. When large unit sizes are being used in hospitals, the contents of the ampoule should be dissolved in water or saline so that the final concentration is 5,000 units per cubic centimeter. This solution should be stored under aseptic precautions in the ice box, and made up freshly every day. Solutions for local or parenteral use may be diluted further, depending upon the concentration desired.

"A. *For intravenous injection:*

"1. The dry powder may be dissolved in sterile physiological salt solution in concentrations of 1,000-5,000 units per cc. for direct injection through a syringe.

"2. The dry powder may be dissolved in sterile saline or 5 per cent glucose solution in lower dilution (25-50 units per cc.) for constant intravenous therapy.

"B. *For intramuscular injection:*

"1. The total volume of individual injections should be small, i. e., 5,000 units per cc. of physiological saline. It may also be given by constant intramuscular drip—120,000 in 250 cc.

"C. *For topical applications:*

"1. The powdered form of the sodium salt is irritating to wound surfaces and should not be used.

"2. Solutions in physiological salt solution with a concentration of 250 units per cc. are satisfactory. For resistant or more intense infections this concentration may be increased to 500 units per cc.

"METHODS OF ADMINISTRATION OF PENICILLIN—

"There are three common methods of administering penicillin—intravenous, intramuscular, and topical. Subcutaneous injections are likely to be painful and should be avoided.

"Repeated intramuscular injections may be tolerated less well than repeated or constant intravenous injections. In many cases, however, the intramuscular route may be the one of choice.

"In the treatment of *meningitis, empyema,* and *surface burns of limited extent,* penicillin should be used topically, that is, injected directly into the subarachnoid space, into the pleural cavity, or applied locally in solution containing 250 units per cc.

"DOSAGE—

"The dosage of penicillin will vary from one patient to another depending on the type and severity of infection. In our experience recovery has followed in many serious infections following 40,000 to 50,000 Oxford units a day, in others 100,000 to 120,000 or even more is necessary. The objective in every case is to bring the infection under control as quickly as possible. The following recommendations are made at the present time with a full realization that revisions may be necessary as experience accumulates.

"It is well to remember that penicillin is excreted rapidly in the urine so that following a single injection it is often impossible to detect it in the blood for a period longer than two to four hours. It is well, therefore, to use repeated intramuscular or intravenous injections every three or four hours, or to administer it as a continuous infusion.

"A. *In serious infections with or without bacteremia* an initial dose of 15,000 or 20,000 Oxford units with continuing dosage as:

"1. Constant intravenous injection of normal saline solution containing penicillin so that 2,000 to 5,000 Oxford units are delivered every hour, making a total of 48,000 to 120,000 units in a 24-hour period. One-half the total daily dose may be dissolved in a liter of normal saline solution and allowed to drip at the rate of 30 to 40 drops per minute.

"2. If continuous intravenous drip is undesirable, then 10,000 to 20,000 units may be injected intramuscularly every three or four hours.

"3. After the temperature has returned to normal the penicillin may be stopped and the course of the disease followed carefully.

"B. *In chronically infected compound injuries, osteomyelitis, etc.,* the dosage schedule should be 5,000 units every two hours or 10,000 units every four hours parenterally with local treatment as indicated. This dosage schedule may have to be increased, depending upon the seriousness of the infection, and response to treatment. The best results are obtained in these cases when penicillin is combined with adequate surgical treatment.

"C. *Sulfonamide-resistant gonorrhea:*

"1. 20,000 units every three hours intramuscularly for 5 doses. The minimum dosage has not been worked out completely. The results of treatment should be controlled by culture of exudate.

"D. *Empyema:*

"1. Penicillin in normal physiological saline solution should be injected directly into the empyema cavity after aspiration of pus or fluid. This should be done once or twice daily, using 30,000 or 40,000 units depending upon the size of the cavity, type of infection and number of organisms. Penicillin solutions should not be used for irrigation. It requires at least six to eight hours for a maximum effect of penicillin.

"E. *Meningitis:*

"1. Penicillin does not penetrate the subarachnoid space in appreciable amounts, so that it is necessary to inject penicillin into the subarachnoid space or intracisternally in order to produce the desired effect. Ten thousand units diluted in physiological saline solution in a concentration of 1,000 units per cc. should be injected once or twice daily, depending upon the clinical course and the presence of organisms.

"F. *Bacterial Endocarditis:*

"Penicillin is the best agent available for the treatment of bacterial endocarditis. Penicillin alone is as effective as penicillin combined with heparin. The treatment should be continued for three weeks or longer depending upon the individual case. The intramuscular route is the one of choice, although in a few instances it may be desirable to use the continuous intravenous route in order to obtain the maximum effect. The dosage should range from 200,000 to 300,000 units a day if the best results are to be obtained."

Conclusion

In the many cases studied by accredited investigators, the above schedule has proved to be adequate. The Civilian Penicillin Distribution Unit, War Production Board, requests medical practitioners employing penicillin to carefully observe the recommendations stated above as to indications, contra-indications, modes of administration and dosage in order to gain the maximum value from the limited supply of penicillin.

ECONOMIC REALITIES

COMPETITION LIMITED!

By Karl Scholz, Ph. D.*

OUR economy is often referred to as a freely competitive society, or one characterized by free competitive enterprise. Much lip service has been rendered to the ideal of free competition by the protagonists of capitalism. Yet even a superficial examination into present day realities reveals that in many branches of industrial activity in the United States, both before the war and during the war, active competition was, and still is, conspicuous by its absence.

Moreover, the semblance of competitive activity is often in the nature of rivalry among industrial giants for consumers' dollars. It is not the kind of rivalry among sellers of identical products assumed under free competitive conditions. Theoretically pure competition exists when no one seller is able to influence the market price appreciably, because of the smallness of his contribution to total sales of competitive products. In our present day world of reality, imperfect, or monopolistic competition, with varying degrees of monopoly control over supply and market price, is typical in many fields of business activity.

Absence of active price competition is reflected in such practices as basing point pricing, resale price fixing, price leadership, various forms of price discrimination and the like, which have commonly been resorted to in our peacetime economy. They all reveal a degree of monopolistic control, which has been exercised by big business.

Nor has the concentration of economic power and the limitation of active competition been appreciably altered in our war economy. This is indicated in the Report of the Director of Contract Settlement, made to Congress in October, 1944. Of an estimated 65 billion dollars of outstanding prime contracts for war goods yet to be delivered, approximately 55 billion dollars, or 85 per cent of the total, are held by 100 corporations and their subsidiaries. Moreover, ten large cor-

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porations and their subsidiaries have prime contracts for 29 billion dollars of undelivered war materials.

Obviously, whatever competition for Government orders may exist among industrial giants in our war economy is not the type of competition that is implied when we speak of a freely competitive society. It would be rather unrealistic to assume that after the war we can put the eighteenth century ideal of free competition into practice by an organized attack on "big business," designed to break it up. It would be more in accordance with present day economic realities to recognize the decline of pure competition and the unmistakable trend toward monopolistic competition among an ever-expanding number of business enterprises.

What is the real economic significance of this trend? An answer to this question necessitates an understanding of the economic implications of imperfect or monopolistic competition, as contrasted with free competition. Monopolistic competition implies that sellers are offering products for sale, which in the minds of buyers are different from possible alternative substitute products. Standard brands and trade-marked articles, sold under various trade names, such as Chesterfields, Squibb, Colgate, and the like, are differentiated in the opinion of buyers from other similar products.

Because of both real and fancied product differentiation in the minds of buyers, usually induced by effective advertising and salesmanship, sellers can, within limits, dictated primarily by the desire to maximize profits or minimize losses, set their own market prices. They are not compelled to sell at market prices over which they have no significant control, as would be the case if they sold in freely competitive markets. Prices set under conditions of monopolistic competition are apt to be somewhat higher than they would be under idealistic conditions of competition.

In consequence, the pattern of income distribution is also somewhat different from what it would be under conditions of pure competition, where market values in the long run tend to equal unit costs of production. These costs, paid to labor and owners of capital and natural resources, represent their income, which under pure competion would be equal to the value of the goods produced, and monopoly profits, as a share of income, would tend to disappear. Those who make differential profits under freely competitive conditions do so because they can keep their costs below those of their competitors and

attract customers by rendering better service. But those who enjoy a monopoly position in the sale of their products can also make profits by restricting output with a view to raising price. They make profits not because of productive services but in spite of them. We must not forget that whenever anyone gets something for nothing, unless it be charity, someone else, of necessity, must get nothing for something.

There is still another aspect to the problem of monopolistic competition in our economy. When business recession sets in, as in the early thirties, those concerns which enjoy a strategic market position are apt to reduce output rather than lower prices significantly, while in those fields of production where there is still a high degree of competition, as for example in agriculture, output is apt to continue at relatively high levels in periods of business depression, with disproportionately large declines in prices. From 1929 to 1932 the prices of farm implements declined around 10 per cent, and those of new motor vehicles scarcely at all, while production of these items came almost to a standstill. The same was true of iron and steel prices and production.

But not so in the case of competitively produced farm products. Here production remained at almost the same level from 1929 to 1932, while prices declined 50 per cent. When individual farmers saw the market prices for their crops decline, many figured that to increase their income, all that was necessary was to raise and sell more crops. But when this became the general practice, it was found to be analogous to working oneself out of house and home. The harder the farmers worked and the more they produced, the more farm prices declined. This price decline was accentuated in the face of decreased demand for farm products during the years of the depression. The individual farmer, who was selling in competitive markets and had no appreciable influence on market price, discovered, to his dismay, that the harder he worked the less he got. Not until the Government came to the aid of farmers and helped them exercise a certain amount of economic birth control, were they able to get more by producing less. What monopolistic competition made possible for industrial concerns, because of their control over supply and price, the Government helped the farmers to achieve.

The consequences of all such practices of curtailment of production are rather obvious. We cannot all have more by producing less. If therefore we would face economic realities in the postwar period

of economic reconstruction we must focus our thinking on devising ways and means for expansion of production and wider distribution of income, rather than seeking to solve our economic difficulties by restriction of output. Too many people have been talking of an economy of abundance. But both abundance and scarcity are relative terms, related to human wants. In the postwar period most of us will be practicing an abundance of economy, rather than reveling in an economy of abundance.

In the face of monopolistic conditions in our economy we can only hope that enlightened self-interest will induce business concerns, enjoying monopolistic market advantages, to aim at large turnover, wider markets, lower prices and small margins of profit per unit, rather than restrict output and maintain relatively high prices, with a view to maximizing profits or minimizing losses. A higher degree of flexibility of costs and prices than has existed in the recent past in our economy will help to diminish the severity of business depressions in the future. In the absence of active price competition in many branches of our economy, the element of price flexibility, assumed under conditions of pure competition, will have to be provided by industry itself as a matter of voluntary choice, based on better understanding of the consequences of monopolistic practices. The alternative is ever expanding governmental direction and guidance of our economic destinies, for pure competition is distinctly limited in our present day economy.

SELECTED ABSTRACTS

Solustibosan in the Treatment of Kala-Azar. H. L. Chung, C. W. Wang and C. U. Lee. *Chinese Med. J. 62,* 17 (1944). Solustibosan, which is a pentavalent antimony compound of hexonic acid, was administered in the treatment of 24 cases of kala-azar. The drug was available in a colorless, stable, aqueous solution representing 20 mg. of metallic antimony per cc.

In all of the cases treated *Leishmania donovani* was demonstrated in the material aspirated from the sternal marrow or from the spleen prior to the start of therapy. The drug was administered intramuscularly in all except two cases; in the latter it was given intravenously. The dosage varied from 6 cc. to 12 cc. on alternate days in most of the cases, though some patients daily doses in the earlier part of the treatment.

In this series of cases there were 17 permanent cures (without relapse in 1-3 years) and 5 immediate cures (diagnostic punctures negative for L. D. bodies at the conclusion of treatment, and no sign of relapse within 2 to 6 weeks). Of the remaining two cases, one was regarded as having received insufficient treatment, and the other as a failure of therapy.

Solustibosan was found to possess low toxicity. In one case its administration was followed by pain in the epigastrium and legs, and in another by generalized urticaria, but in all other cases no toxic symptoms attributable to the drug were noted.

The Use of Honey in the Treatment of Chilblains, Non-Specific Ulcers and Small Wounds. A Preliminary Report. K. L. Yang, *Chinese Med. J. 62,* 55 (1944). An ointment consisting of 80 per cent of honey in a base of vaseline or lard was employed with marked success in the treatment of 50 cases of chilblains, chilblain ulcers, ordinary ulcers and small wounds.

This combination was employed in the hope that it might prove an acceptable substitute for ointments containing cod liver oil, a product which had become difficult to obtain because of the war. It

was thought that honey might be bacteriostatic because of its high sugar content, and that it might contain vitamin A because its yellow pigment is derived from various yellow flowers.

In this group of cases the application of honey ointment produced complete cures in 76 per cent of the cases, marked improvement or partial cure of multiple lesions in 20 per cent, and no improvement in 4 per cent. The following effects were noted: (1) rapid subsidence of passive congestion and edematous swelling; (2) a rapid stimulation of epithelization and granulation; (3) in some cases a rapid diminution of local pain; and (4) the presence of a moderate amount of seropurulent discharge did not interfere with its effectiveness.

It was not necessary to change dressings frequently, especially when the lesions were clean and dry.

It is believed that the presence of small amounts of formic acid, sulfur, chlorine, and metallic elements in honey is of no significance in explaining its action. From an examination of the literature available on the vitamin A content of honey the author concludes that this is an uncertain point.

The Histology of Belladonna Root. Part I. Atropa Belladonna Linn. C. Melville. *Quart. J. Pharm. & Pharmacol. 17,* 201 (1944). The histology of the root, rootstock, stem base and stolon of *Atropa Belladonna* is described and illustrated. The investigation was performed on the commercial drug and on fresh material from plants which were one, three, and five years old.

The rootstock, stem base and stolon exhibit anatomical differences from the root in that they possess a pericycle, a perimedullary phloem and a pith. Scattered groups of lignified fibers occur in the first two of these tissues; in the rootstock and stolon these fibers are septate and up to about 4.5 mm. in length, whereas in the stem base they are simple and up to about 2 mm. in length. Certain cells of the phelloderm, secondary phloem and pith of the rootstock, and of the cortex of the stem base, are lignified. The xylem of the rootstock and stem base consists of a dense woody cylinder, in contrast to its character in the root and stolon.

Anatomical differences existing between the elements composing the xylem of the several organs and the root are described.

Vitamin K Therapy in Menorrhagia. R. Gubner and H. E. Ungerleider. *Clinical Med. 51,* 321 (1944). Previously published observations by the authors indicate that vitamin K therapy is useful in controlling menorrhagia in cases where this condition is not due to local pelvic disorders.

This paper reports the treatment of 43 cases of menorrhagia by the oral administration of vitamin K. The drug was given in 5 mg. tablets, twenty of these usually constituting a five-day course of therapy. In most cases medication was begun one or two days before the onset of menstruation or else on the first day of the menses. A significant abbreviation of menstrual flow was noted in two-thirds of cases in which the menses were prolonged beyond five days.

Other investigators have shown that the reason menstrual blood fails to clot is that clotting occurs regularly in utero, and that menstrual blood is in reality serum lacking in prothrombin and fibrinogen.

The Stability of Preparations Containing Ethyl Nitrite. A. H. A. Abbott and B. H. Hooper. *Quart. J. Pharm. & Pharmacol. 17,* 177 (1944). Liquor Aethylis Nitritis Concentratus, recognized in the Fifth Addendum to the B. P. 1932, is required to contain from 17 to 20 per cent w/v of ethyl nitrite after storage; after the container has been opened occasionally the solution must contain not less than 10 per cent of the ester.

The stability of this preparation under 4 varying conditions of storage up to 90 days was studied by the periodic examination of samples contained in 4-ounce glass-stoppered, amber bottles. It was found that the rate of decomposition was relatively slow and that it was not markedly influenced by the conditions of storage.

It was found that a mixture of 1 volume of the concentrated solution and 7 volumes of water, a preparation authorized as an alternative for Spiritus Aetheris Nitrosi B. P. 1932, contained only about 50 per cent of the calculated amount of ethyl nitrite immediately after making the dilution. The loss of ethyl nitrite was considerably reduced when the water was replaced by 95 per cent ethyl alcohol. The gasometric method of analysis described for Spiritus Aetheris Nitrosi B. P. was used for strongly alcoholic solutions; for solutions containing a large proportion of water the volumetric procedure of the Ph. Nederlandica V. was employed.

Storage tests on the stability of ethyl nitrite in various solvents, and on these solutions after dilution with water, indicated that a solution of the ester in isopropyl alcohol containing 5 per cent v/v of glycerin was superior to the others examined, which included the following: (1) Spiritus Aetheris Nitrosi B. P. 1932; (2) a spirit containing the ester in equal volumes of absolute alcohol and glycerin; (3) Liquor Aethylis Nitritis B. P. 1914, containing 5 per cent v/v of glycerin in absolute alcohol; (4) a solution of the ester in equal volumes of absolute alcohol and glycerin; (5) a solution of the ester in equal volumes of isopropyl alcohol and propylene glycol; and (6) a solution of the ester in equal volumes of absolute alcohol and propylene glycol.

The Histology of Belladonna Root. Part II. Indian Belladonna. C. Melville. *Quart. J. Pharm. & Pharmacol. 17,* 213 (1944). Indian belladonna root is recognized by the Fifth Addendum to the B. P. 1932 as the root of *Atropa acuminata* Royle ex Lindley, with a limit of 25 per cent of rootstock and stem base. This paper describes and illustrates the histology of the root, rootstock, stem base and stolon of the commercial dried drug.

A pericycle, a perimedullary phloem and a pith occur in the rootstock, stem base and stolon, but not in the root. Lignified septate fibers are present in the pericycle and perimedullary phloem. The secondary xylem of the stem base forms a single dense hollow woody cylinder, whereas in the remaining organs there are several such cylinders arranged concentrically.

The characters which distinguish the several organs from the root are enumerated.

Indian belladonna root possesses the following characters which serve to distinguish it from the root of *A. Belladonna:*

1. The cork cells are longer and the number per unit area is less. A mean value of less than 344 cells per sq. mm. calculated from 10 fields of about 0.1 sq. mm. indicates Indian belladonna; over 347 cells per sq. mm. indicates *A. Belladonna.*
2. Fibres and fibrous cells occur in the secondary phloem.
3. The vessel elements are longer.
4. The xylem fibers are longer and more numerous.
5. Starch grains of more than three components are absent.

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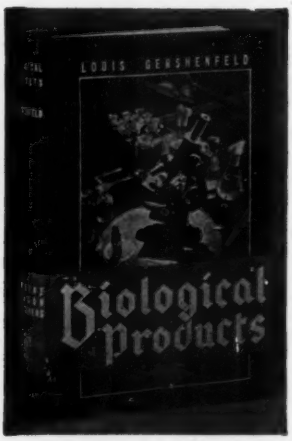

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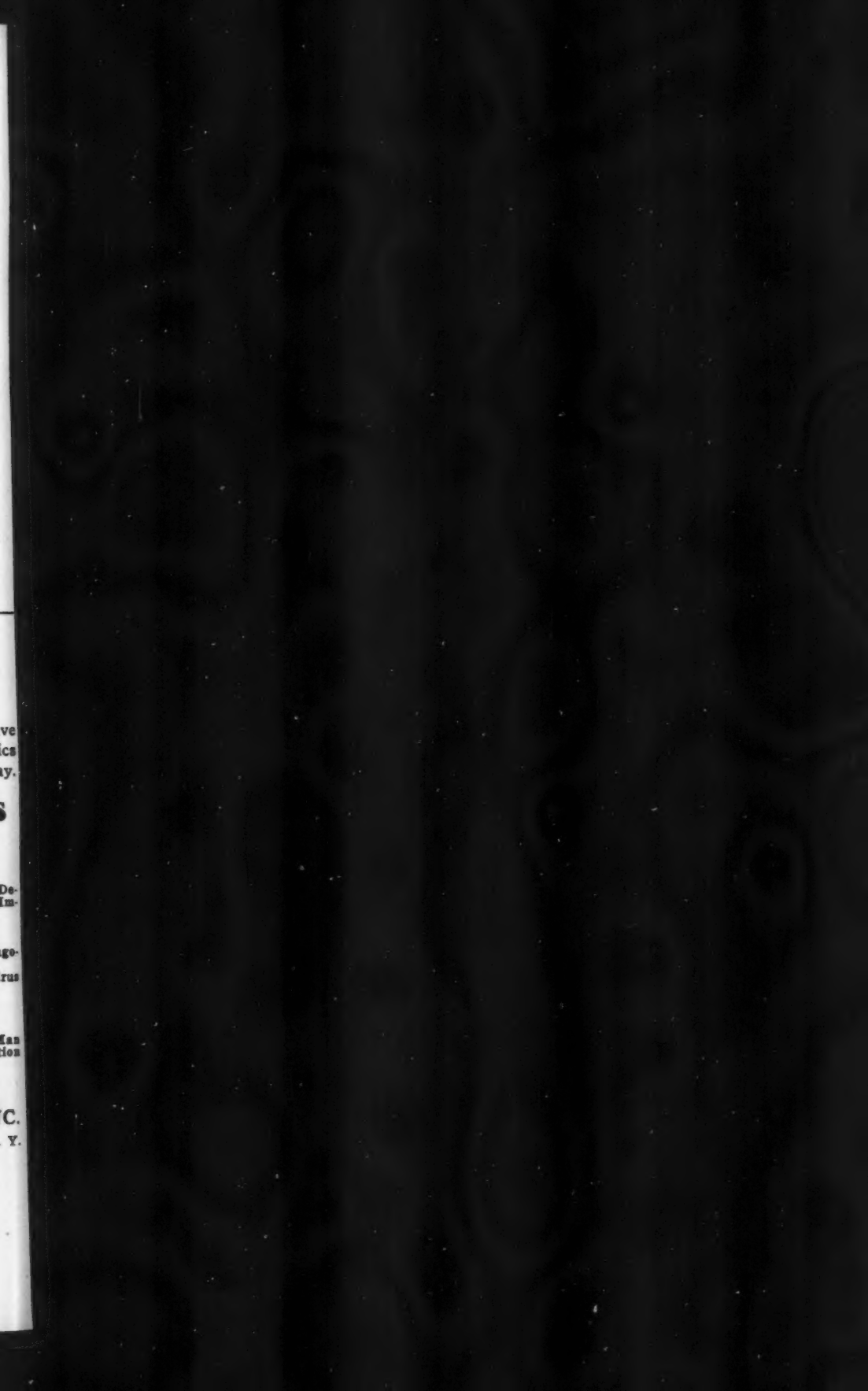

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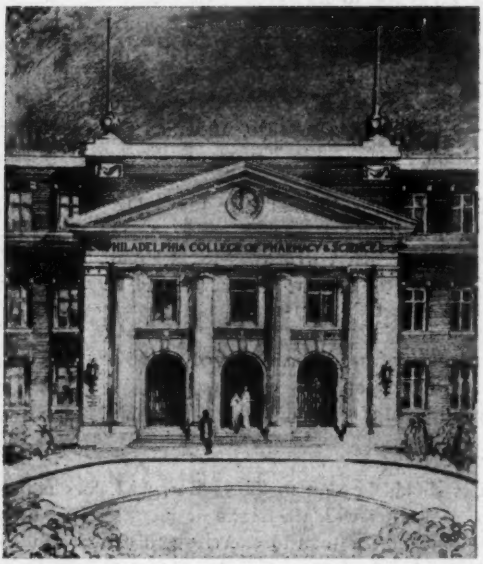

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